Citation:

Whelton PK, Appel LJ, Espeland MA, Applegate WB, Ettinger WH, Kostis JB, Kumanyika S, Lacy CR, Johnson KC, Folmar S, Culter JA. Sodium Reduction and Weight Loss in the Treatment of Hypertension in Older Persons; A Randomized Controlled Trial of Nonpharmacologic Interventions in the Elderly (TONE). TONE Collaborative Research Group.*JAMA* 1998 Mar 18; 279 (11): 839-846. Erratum in: *JAMA* 1998 Jun, 24; 279 (24): 1954

PubMed ID: 9515998

Study Design:

Randomized controlled study

Class:

A - Click here for explanation of classification scheme.

Research Design and Implementation Rating:

POSITIVE: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

To determine whether weight loss or reduced sodium intake is effective in the treatment of older persons with hypertension.

Inclusion Criteria:

- Men and women 60 to 80 years old with an average systolic BP less than 145mm Hg and diastolic BP less than 85mm Hg (mean of nine measurements; three at each of three visits) while taking a single anti-hypertensive medication or a single combination regimen consisting of a diuretic agent and a non-diureticagent.
- Individuals taking two anti-hypertensive medications were enrolled if they could be successfully weaned to one anti-hypertensive medication during the screening phase
- Willingness of an enrollee and his or her physician to participate
- Stable health
- Independence in activities of daily living
- Presumed capacity to alter diet
- Physical activity in accordance with the requirements of any TONE intervention.

Exclusion Criteria:

- History of a heart attack or stroke within the preceding six months
- Current angina pectoris
- Congestive heart failure
- Insulin dependent diabetes mellitus

- Serious mental or physical illness
- Unexplained or involuntary weight loss of 4.5kg or greater during the previous year
- Body mass index less than 21kg/m^2 in men or women or greater then 33kg/m^2 in men or greater than 37kg/m^2 in women
- Presumed inability to comply with the protocol
- Hypercreatinemia (greater than 152umol/L {greater than 2.0mg/dL})
- Hyperkalemia (greater than 5.5mmol/L)
- Hyperglycemia (non-fasting level greater than 14.4mmol/L {greater than 260mg/dL})
- Anemia (hemoglobin level less than 110g/L).

Description of Study Protocol:

Recruitment

The study was conducted as a multicenter, controlled clinical trial in which participants were randomly assigned to one of six treatment cells across two strata of body weight. Details of the recruitment experience have been published. (see reference 15)

Design

The trial was designed to test the following two hypotheses:

1. Prescribing a sodium reduction program for obese and non-obese older patients with hypertension reduces the rate of primary end points following the withdrawal of BP-lowering medications
2. Prescribing a weight loss program for obese individuals reduces the rate of primary end points following the withdrawal of BP-lowering medications.

Blinding used

Outcome information was obtained by staff members who were blind to the participants's intervention assignment

Intervention

- Small group and individual meetings with nutritionists and exercise counselors in which participants were advised on ways to change eating patterns and increase physical activity (for weight loss with or without sodium reduction)
- Adapt the TONE lifestyle recommendations to their individual circumstances.

Statistical Analysis

- Analysis of variance tests for continuous variables and X2 tests for discrete variables to highlight comparisons for which the randomization algorithm yielded a chance imbalance
- Outcome analyses were conducted on an intentiona-to-treat basis using two-sided significance levels of .05
- Kaplan-Meier curves were used to compare times to end points and each hypothesis was tested using Cox proportional hazards regression models
- Relative hazard ratios were used to summarize the impact of treatment assignment on the rate of end points over time
- Intervention related BP changes from baseline to follow-up were assessed using Laird-Ware models to average BPs after intervention assignment and prior to drug withdrawal
- Likelihood ratio statistics and SEs were used to perform inference testing (SAS/STAT

software, release 6.06, SAS Institute Inc. Cary, North Carolina)
- Contrasts among the proportions of participants experiencing one or more events were evaluated using the Fisher exact test.

Data Collection Summary:

Timing of Measurements

Baseline and quarterly from August 1992 until December 1995 medical history including medication information and symptoms, measurements of body weight and BP. 24 urine collections were obtained twice during the enrollment period and at the nine-month, 18-month and final closeout visits for measurement of sodium content. A 24-hour dietary recall history was obtained by a trained technician twice during enrollment and at the nine- and 12-month follow-up visits and every six months thereafter.

Dependent Variables

- Body weight
- Blood pressure
- Anti-hypertensive medication use.

Independent Variables

- Dietary sodium intake
- Eating patterns and physical activity
- Knowledge and behavior skills necessary to achieve and maintain their desired reductions in sodium intake and body weight.

Description of Actual Data Sample:

Initial N

N=975 (585 obese and 390 non-obese)

Attrition (final N)

N=975

Age

60 to 80 years old; 78% between 60 to 69 years of age

Ethnicity

White and African American

Anthropometrics

Baseline characteristics similar in each group except that there were slightly more men in the sodium reduction and weight loss combined group than in the three other groups in the obese stratum.

Location

Wake-Forest University School of Medicine, Winston-Salem, North Carolina

Johns Hopkins University School of Hygiene and Public Health, Baltimore, Maryland

University of Tennessee-Memphis

Robert Wood Johnson Medical School, New Brunswick

Summary of Results:

Results

BP results

- Systolic and diastolic BP did not differ across treatment groups at baseline, but at the last visit before medication withdrawal was attempted the mean systolic and diastolic BP values were significantly lower in all the intervention groups than in the usual care group
- The percentages for BP control at the goal of less than 140/90mm Hg were 71% for those assigned to sodium reduction, 63% for weight loss, 73% for sodium reduction and weight loss combined and 65% for usual care.

Body weight

The average reduction in weight for the participants assigned to weight loss was approximately 3.5 to 4.5 kg resulting in net reductions of 3.8 (95% CI, 3.1-4.5), 3.6 (95% CI, 2.8-4.3) and 3.9 (95% CI, 2.7-5.1) kg at the nine, 18 and 30-month follow-up visits, respectively ($P<0.01$ for all), vs. an average 0.9kg reduction (95% CI, 0.4-1.3) for those not assigned to weight loss.

Withdrawal of anti-hypertensive medication

Anti-hypertensive medication could be stopped in 86.8% of those assigned to usual care in 92.6% assigned to sodium reduction alone, in 93.2% assigned to weight loss alone and in 93.2% assigned to weight loss and sodium reduction combined.

Author Conclusion:

The Tone study is the first trial of sufficient size and duration to provide convincing evidence regarding the feasibility, efficicacy and safety of dietary lifestyle interventions as a means to control high BP and decrease the need for anti-hypertensive medication in older patients with hypertension.

Reviewer Comments:

The positive study results should encourage more clinical trials.

Research Design and Implementation Criteria Checklist: Primary Research

Relevance Questions

1.	Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies)	Yes
2.	Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	Yes
3.	Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice?	Yes
4.	Is the intervention or procedure feasible? (NA for some epidemiological studies)	Yes

Validity Questions

1.	**Was the research question clearly stated?**	Yes
1.1.	Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified?	Yes
1.2.	Was (were) the outcome(s) [dependent variable(s)] clearly indicated?	Yes
1.3.	Were the target population and setting specified?	Yes
2.	**Was the selection of study subjects/patients free from bias?**	???
2.1.	Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	Yes
2.2.	Were criteria applied equally to all study groups?	Yes
2.3.	Were health, demographics, and other characteristics of subjects described?	Yes
2.4.	Were the subjects/patients a representative sample of the relevant population?	???
3.	**Were study groups comparable?**	Yes
3.1.	Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	???
3.2.	Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	Yes
3.3.	Were concurrent controls used? (Concurrent preferred over historical controls.)	Yes

3.4.	If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	N/A
3.5.	If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	N/A
3.6.	If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	N/A
4.	**Was method of handling withdrawals described?**	N/A
4.1.	Were follow-up methods described and the same for all groups?	Yes
4.2.	Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	N/A
4.3.	Were all enrolled subjects/patients (in the original sample) accounted for?	Yes
4.4.	Were reasons for withdrawals similar across groups?	N/A
4.5.	If diagnostic test, was decision to perform reference test not dependent on results of test under study?	N/A
5.	**Was blinding used to prevent introduction of bias?**	Yes
5.1.	In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	No
5.2.	Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	Yes
5.3.	In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	N/A
5.4.	In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	N/A
5.5.	In diagnostic study, were test results blinded to patient history and other test results?	N/A
6.	**Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were interveningfactors described?**	Yes
6.1.	In RCT or other intervention trial, were protocols described for all regimens studied?	Yes
6.2.	In observational study, were interventions, study settings, and clinicians/provider described?	N/A

6.3.	Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	Yes
6.4.	Was the amount of exposure and, if relevant, subject/patient compliance measured?	Yes
6.5.	Were co-interventions (e.g., ancillary treatments, other therapies) described?	No
6.6.	Were extra or unplanned treatments described?	No
6.7.	Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	Yes
6.8.	In diagnostic study, were details of test administration and replication sufficient?	N/A
7.	**Were outcomes clearly defined and the measurements valid and reliable?**	Yes
7.1.	Were primary and secondary endpoints described and relevant to the question?	Yes
7.2.	Were nutrition measures appropriate to question and outcomes of concern?	Yes
7.3.	Was the period of follow-up long enough for important outcome(s) to occur?	Yes
7.4.	Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	Yes
7.5.	Was the measurement of effect at an appropriate level of precision?	Yes
7.6.	Were other factors accounted for (measured) that could affect outcomes?	No
7.7.	Were the measurements conducted consistently across groups?	Yes
8.	**Was the statistical analysis appropriate for the study design and type of outcome indicators?**	Yes
8.1.	Were statistical analyses adequately described and the results reported appropriately?	Yes
8.2.	Were correct statistical tests used and assumptions of test not violated?	Yes
8.3.	Were statistics reported with levels of significance and/or confidence intervals?	Yes
8.4.	Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	???
8.5.	Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	Yes
8.6.	Was clinical significance as well as statistical significance reported?	Yes

8.7.	If negative findings, was a power calculation reported to address type 2 error?	N/A
9.	**Are conclusions supported by results with biases and limitations taken into consideration?**	Yes
9.1.	Is there a discussion of findings?	Yes
9.2.	Are biases and study limitations identified and discussed?	Yes
10.	**Is bias due to study's funding or sponsorship unlikely?**	Yes
10.1.	Were sources of funding and investigators' affiliations described?	Yes
10.2.	Was the study free from apparent conflict of interest?	Yes